www.jcimcr.org

JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 5

An interesting case of anti-GAD65 encephalitis

Kyle Wong[1]*; Abhay Venkat[2]

[1]Neurology Registrar, The Wollongong Hospital, NSW, Australia.

[2]Consultant Neurologist, The Wollongong Hospital, NSW, Australia.

***Corresponding Author: Kyle Wong**

Neurology Registrar, The Wollongong Hospital, NSW, Australia.

Tel: +612 4222 5000; Email: kyle_wong@live.com

Received: Nov 02, 2024

Accepted: Nov 20, 2024

Published: Nov 27, 2024

Archived: www.jcimcr.org

Copyright: © Wong k (2024).

DOI: www.doi.org/10.52768/2766-7820/3360

Abstract

We present the case of an 18 year old female who presented with short term amnesia, palpitations and headaches with no significant past medical history. Examination revealed inability to recall three objects, autonomic dysfunction and no focal neurological deficit. She was initially treated with intravenous antibiotics and antiviral medication to cover for infectious causes of encephalitis. She was also treated with IV antiepileptic medication after her EEG demonstrated epilepsy partials continua. She later received intravenous steroids and intravenous immunoglobulin for treatment of presumed autoimmune encephalitis once infection was ruled out. She proceeded to second line immunosuppression with mycophenolate and rituximab. Her antineuronal antibodies in her cerebrospinal fluid later returned positive for anti-Glutamic Acid Decarboxylase 65 (GAD-65). At follow up at 1 month and 6 months, our patient had significant recovery in her memory and cognitive function. We postulate early immunosuppression pending antibody results was key to her good outcome.

Keywords: Autoimmune encephalitis; Anti-glutamic acid decarboxylase 65; Anti-GAD65; Limbic Encephalitis.

Abbreviations: GAD: Anti-glutamic acid decarboxylase; ANNA: Anti-Neuronal Nuclear Antibody; CRP: C-Reactive Protein; CSF: Cerebrospinal Fluid; CRMP: Collapsing Response Mediator Protein; CASPR2: Contacting Associated Protein Like 2; DPPX: Dipeptidyl-Peptidase-Like Protein-6; EEG: Electroencephalogram; FLAIR: Fluid Attenuated Inversion Recovery; GABA: Gamma-Amino Butyric Acid; IgLON5: Iglon Family Member 5; LGI-1: Leucin-Rich Glioma Inactivated 1; MRI: Magnetic Resonance Imaging; MCV: Mean Corpuscular Volume; NMDA: N-Methyl-D-Aspartate; PNMA: Paraneoplastic Ma Antigen; PCR: Polymerase Chain Reaction; PCA: Purkinje Cell Cytoplasmic Antibody; SOX-1: Sry-Box Transcription Factor 1; WCC: White Cell Count.

Introduction/background

Encephalitis is a severe inflammation of the brain parenchyma with many different causes including both infectious and autoimmune [1]. It is a condition that can be both difficult to diagnose and treat. Anti-glutamic acid decarboxylase 65 (GAD65) is a rare cause of autoimmune limbic encephalitis that can present in young women with new onset seizures [1]. Prognosis is generally poor with persistent seizures and cognitive impairment experienced by the majority of patients. We present the case of a young 18 year old female with an excellent neurological recovery following her episode of anti-GAD 65 encephalitis. We postulate early treatment with immunosuppression prior to her autoantibody results becoming available led to her good outcome.

Case presentation

An 18 year-old female presented to hospital with short term amnesia, palpitations and headaches. She recently presented to the hospital emergency department 10 days prior with complaints of palpitations, chest tightness and anxiety with no prior history of a mood disorder. Collateral history from her brother revealed sudden onset new confusion, amnesia and fevers two weeks prior. There was no history of a flu-like illness or gastrointestinal illness prior. She describes a rising feeling and a sense of uneasiness that were coupled with episodes of palpitations. The family report that her memory impairment was so severe that she could not remember events or conversations that occurred even minutes prior. She has no significant past medical history and is not on any regular medications. She does not have any known allergies and does not have any significant family history of neurological or autoimmune disorders. She resides with her mother, sister and brother at home and works in childcare. She migrated from the Democratic Republic of Congo to Australia at the age of 15 having spent 13 years of her life in refugee camps. On examination she exhibited a significant amnesia with inability to immediately recall three objects. Rowland Universal Dementia Assessment Scale (RUDAS) was 13/30-primarily losing points for episodic memory, executive function, and constructional praxis. She had an unremarkable neurological examination with no focal deficits. Of note was autonomic dysfunction with intermittent sinus tachycardia with a heart rate fluctuating up to 140 beats per minute and significant postural drop that was greater than 30 mmHg in her systolic blood pressure. Her cardiorespiratory examination was unremarkable otherwise.

Differential diagnosis: The differential diagnosis at the time of admission was encephalitis, the causes of which included infective (e.g. herpes vs bacterial or fungal/tuberculosis given her background) and autoimmune encephalitis (limbic or paraneoplastic). Other causes included first presentation of an organic psychiatric illness or a functional neurological disorder.

Investigations: She was hyponatremic (Na 129 mmol/L), thrombocytopenic ($129x10^9$/L) with a microcytosis (MCV 78 fL). Her inflammatory markers were not elevated with a normal CRP (<1 mg/L) and WCC ($6.6x10^9$/L). Her cerebrospinal fluid studies revealed 2 red cells, 0 polymorphs, 9 mononuclear cells. Her CSF protein was normal at 0.17 g/L and the CSF glucose was normal at 4.8 mmol/L (paired serum glucose 8.2 mmol/L). Oligoclonal bands were present in serum and CSF. There were no organisms seen on microscopy and no growth on culture. CSF PCR studies for varicella zoster virus, herpes simplex virus type 1 and 2, human herpesvirus type 6 DNA, enterovirus, Epstein Barr virus, cytomegalovirus was negative. TB and fungal culture were negative. Respiratory viral swabs for COVID19, respiratory syncytial virus and influenza were negative. A repeat lumbar puncture one week post admission was done to exclude an early false negative HSV PCR which revealed a persistent pleocytosis with 5 red cells, 0 polymorphs and 5 mononuclear cells and negative HSV PCR. She proceeded to have an Electroencephalogram (EEG) which showed epilepsy partials continua with a left temporal predominance and non-convulsive status epilepticus. An MRI brain showed symmetrical hyperintensity of the medial temporal lobes with non-specific oedema affecting the hippocampus and amygdala (Figure 1). An US pelvis, MRI pelvis, positron emission tomography and mammography did not show any evidence of malignancy.

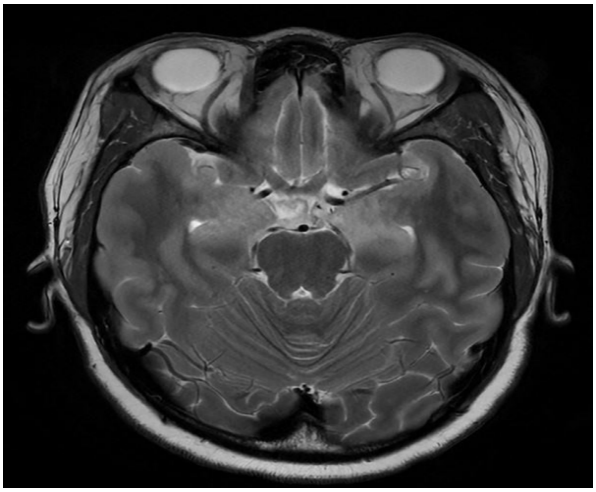

Figure 1: MRI (Axial T2 Flair) demonstrating hyperintensity of bilateral medial temporal lobes consistent with encephalitis.

We awaited results from the limbic and autoimmune encephalitis panel.

Treatment

Pending autoimmune and infectious serology, our patient was initially treated with a course of IV ceftriaxone and IV acyclovir to empirically treat for meningitis. This was later ceased when her cultures and PCR returned negative. She was started on levetiracetam 1.5 g BD in addition to lacosamide 200 mg BD. Her repeat EEG continued to show evidence of ongoing epilepsy partials continua and she proceeded to a midazolam infusion for 72 hours before being switched to clonazepam and then later clobazam 10 mg nocte. From an immunosuppression point of view, she was initially treated with IV methyl prednisone 1 g daily for 5 days followed by 50 mg oral prednisone as well as Intravenous Immunoglobulin (IVIG) 2 g/kg to treat for autoimmune encephalitis. She proceeded to second line immunosuppression therapy with mycophenolate 1000 mg BD, and rituximab 1 g at day 1, day 14 and 3 months. She is maintained on IVIG 0.4 g/kg monthly.

Outcome and follow-up: The anti-neuronal antibodies in CSF returned 'Strong positive' for anti-GAD65 (only qualitative testing was available at author's centre). The serum anti-GAD65 titre was also positive at >2000 U/mL (limit of detection at the author's centre). The remainder of her antibodies including amphiphysin, ANNA1 Hu, ANNA2 Ri, PCA Yo, PNMA2 Ma2/Ta, CV-2 CRMP5, Recoverin, SOX-1, Titin, Zic4, Tr was negative. The limbic encephalitis panel (including neuromyelitis optica, NMDA, CASPR2, LGI-1, GABA-B, DPPX and IgLON5) returned negative on both serum and CSF. Myelin Oligodendrocyte (MOG) antibody was negative. Serial EEGs done throughout her admission demonstrated improvement with resolution of electrographic seizures. A repeat RUDAS done one week after the initial test was static at 13/30. Our patient developed steroid induced diabetes and was commenced on gliclazide modified release 60 mg BD, metformin 1000 mg extended release daily with supplemental subcutaneous insulin. She was commenced on prophylactic trimethoprim-sulfamethoxazole for pneumocystis jiroveci pneumonia prevention. She was also started on ivabradine 2.5 mg BD for autonomic tachycardia. She was deemed safe for discharge with the plan to wean her prednisone by 5 mg every fortnight to a target dose of 25 mg daily, continue

monthly IVIG, complete her course of rituximab and to follow up with her neurologist as an outpatient. On follow up 1 month later she was noted to have a dramatic improvement in cognition and mood. RUDAS assessment had improved to 27/30, dysautonomia had resolved and MRI showed reduced intensity of the FLAIR changes in both temporal lobes. EEG continued to demonstrate bitemporal slowing and sharp wave discharges in the left hemisphere however none reached epileptiform criteria. On repeat follow up 6 months post discharge from hospital, our patient continued to show significant improvement with return to her usual occupation as a childcare worker. She did not have any further seizures or dysautonomia. Her glycaemic control improved (HbA1c 5.3%) and her metformin and gliclazide were ceased. Her antiepileptic medicines were dose reduced. She was continued on mycophenolate 1000 mg BD, 6 monthly maintenance IVIG and prednisone 5 mg daily for immunosuppression. Her repeat serum anti-GAD65 antibody continued to remain positive at >2000 U/mL.

Discussion/conclusion

Encephalitis is a severe inflammatory brain disorder with various causes. In recent years, the emergence of autoimmune causes of encephalitis have been identified. These syndromes are associated with antibodies against neuronal cell surface proteins or synaptic proteins [1]. Our patient presented with several classical features of autoimmune encephalitis including autonomic instability, altered level of cognition, seizures and amnesia. She also showed typical biochemical markers including hyponatremia and CSF pleocytosis. As part of her work up for encephalitis, she returned strongly positive for anti-GAD65 antibodies in both her serum and CSF leading to a diagnosis of anti-GAD65 limbic encephalitis. Glutamic Acid Decarboxylase 65 (GAD-65) is known to convert glutamate into Gamma-Amino Butyric Acid (GABA) in both the beta cells of the pancreas and the central nervous system [2]. It is currently unknown how the presence of these autoantibodies cause disease. It has been postulated that the presence of anti-GAD65 inhibits the action of GAD65 which causes a reduction in inhibitory GABAergic neural networks which, in turn, leads to a state of hyperexcitability in the central nervous system [2]. Anti-GAD65 autoimmunity can present with various distinct clinical syndromes. These include stiff-person syndrome, cerebellar ataxia, epilepsy and encephalitis with medication resistant temporal lobe seizures [3,4]. Overlap syndromes can also occur. Anti-GAD65 antibodies can also be present in type 1 diabetes mellitus, however titres of GAD antibodies are generally lower compared to patients with neurological syndromes [4,5].

It is interesting to note there are several case reports in the literature of patients, especially pediatric patients, presenting with onset of type 1 diabetes mellitus either before, during or after the onset of autoimmune encephalitis [6]. In our case study, our patient developed diabetes requiring both oral medication (metformin and gliclazide) and subcutaneous insulin during her hospitalization with no prior history of this disease. Whilst we have initially attributed her hyperglycemia to her steroid medication, it is possible her hyperglycemia may be secondary to de novo onset of type 1 diabetes mellitus in the setting of her positive anti-GAD65 antibodies. Further autoantibodies for autoimmune diabetes were not pursued during our patient's admission but may have been helpful for further work up of the audiology of her diabetes. Anti-GAD65 limbic encephalitis is uncommon with an estimated prevalence of 1.9/100,000 and to date has largely been described in case reports [5]. First line treatment for anti-GAD65 encephalitis is generally IVIG, high dose steroids or plasma exchange [5]. This is later followed by switching to rituximab or cyclophosphamide if there is deemed to be insufficient clinical response [5]. There are currently no established guidelines for the specific treatment of anti-GAD65 limbic encephalitis and treatment regimens vary based on clinician experience and hospital centres. Anti-GAD65 limbic encephalitis is difficult to treat with up to 80% of patients continuing to experience seizures and 69% experiencing ongoing cognitive impairment [5]. Our patient demonstrated the treatment resistant nature of these seizures as she required multiple antiepileptics and a midazolam infusion to treat her non convulsive status epilepticus seen on her EEG initially. Acknowledging that anti-GAD65 limbic encephalitis is usually refractory and only partially responsive to immunosuppression, we postulate that early aggressive immunosuppressive treatment pending anti-GAD65 antibodies led to her excellent cognitive outcome and control of her seizures. Follow up at both 1- and 6-months post discharge demonstrated this good clinical response was sustained.

Learning points/take home messages

1. Consider a diagnosis of autoimmune encephalitis in patients who present with subacute onset of amnesia, psychiatric symptoms and dysautonomia.

2. If autoimmune encephalitis is being considered, ensure a paired serum and CSF sample is taken and sent for anti-neuronal antibodies, limbic encephalitis antibodies, anti-MOG antibodies to aid in diagnosis.

3. Anti-GAD65 encephalitis is a rare autoimmune encephalitis that presents classically in young women (<30 years of age) with seizures.

4. Awaiting antibody results before immunosuppression results in delayed treatment.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Written and signed consent for publication was provided by the patient.

Availability of data and materials: Not applicable.

Competing interests: The authors have no competing interests to declare.

Funding: Not applicable.

Authors' contributions: Dr Kyle Wong conceived of the article, performed the literature search and wrote the article. Dr Abhay Venkat provided expert guidance and critical revision of the article.

Acknowledgements: Not applicable.

References

1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016; 15(4): 391-404. doi:10.1016/S1474-4422(15)00401-9.

2. Georgieva Z, Parton M. Cerebellar ataxia and epilepsy with anti-GAD antibodies: treatment with IVIG and plasmapheresis. BMJ Case Rep. 2014; 2014: 2013202314. doi:10.1136/bcr-2013-202314.

3. Saiz A, Blanco Y, Sabater L, et al. Spectrum of neurological syndromes associated with glutamic acid decarboxylase antibodies: diagnostic clues for this association. Brain. 2008; 131(10): 2553-2563. doi:10.1093/brain/awn183.

4. Muñoz-Lopetegi A, de Bruijn MAAM, Boukhrissi S, et al. Neurologic syndromes related to anti-GAD65: Clinical and serologic response to treatment [published correction appears in Neurol Neuroimmunol Neuroinflamm. 2020; 7(4). Neurol Neuroimmunol Neuroinflamm. 2020; 7(3): 696. doi:10.1212/NXI.0000000000000696.

5. Dade M, Berzero G, Izquierdo C, et al. Neurological Syndromes Associated with Anti-GAD Antibodies. Int J Mol Sci. 2020; 21(10): 3701. Published 2020 May 24. doi:10.3390/ijms21103701.

6. Kern K, Shuster BA. Rare presentation of anti-GAD-65 antibody-positive autoimmune encephalitis and simultaneous onset of type 1 diabetes mellitus in a paediatric patient. BMJ Case Rep. 2021; 14(3): 237913. doi:10.1136/bcr-2020-237913.